STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 143552

TO: Zohreh Fay **Location: REM/3C70** BA61 **Art Unit: 1614** **Wednesday, February 02, 2005** **Case Serial Number: 09/712612**	**From: Edward Hart** **Location: Biotech-Chem Library** **REM-1A55** **Phone: 571-272-2512** **edward.hart@uspto.gov**

Search Notes

Examiner Fay,

Here are the results of the search you requested.

Please feel free to contact me if you have any questions.

Edward Hart

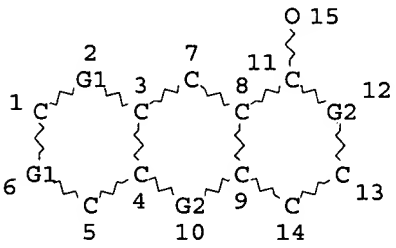
```
=> file hcaplus
FILE 'HCAPLUS' ENTERED AT 15:53:47 ON 02 FEB 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)
```



```
FILE COVERS 1907 - 2 Feb 2005  VOL 142 ISS 6
FILE LAST UPDATED: 1 Feb 2005  (20050201/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d stat que
L1              STR
```




```
VAR G1=C/N/O/S
VAR G2=N/O/S
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC   1
NUMBER OF NODES IS  15

STEREO ATTRIBUTES: NONE
L3          409 SEA FILE=REGISTRY SSS FUL L1
L4           96 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3
L11           0 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4 AND (?CATARACT? OR
                ?RETIN?)


=> d his

     (FILE 'HOME' ENTERED AT 15:24:26 ON 02 FEB 2005)
               SET COST OFF

     FILE 'REGISTRY' ENTERED AT 15:24:39 ON 02 FEB 2005
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```
L1              STR
L2            1 S L1
L3          409 S L2 FULL

     FILE 'HCAPLUS' ENTERED AT 15:36:30 ON 02 FEB 2005
L4           96 S L3
                E DIABETES/CT
L5        10753 S E3
                E E3
                E E3+ALL
                E E2
                E E3
                E E3+ALL
L6        12538 S E5+OLD
                E DIABETES/CT
                E E12+ALL
L7        70973 S DIABETES MELLITUS+OLD/CT
                E E20+ALL
L8        16653 S ANTIDIABETIC AGENTS+OLD/CT
                E US1999-165151/AP,PRN
L9            1 S L4 AND L5-L8
                E EYE DISEASE/CT
                E E4+ALL
                E E2
                E CATARACT
L10        7298 S E3-E5
                E CATARACT/CT
                E E3
                E E3+ALL
L11           0 S L4 AND (?CATARACT? OR ?RETIN?)

     FILE 'HCAPLUS' ENTERED AT 15:53:22 ON 02 FEB 2005

     FILE 'HCAPLUS' ENTERED AT 15:53:47 ON 02 FEB 2005

=> s ibib abs hitrn l9 tot
MISSING OPERATOR HITRN L9
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> d ibib abs hitrn l9 tot

L9   ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2001:739571  HCAPLUS
DOCUMENT NUMBER:          137:15586
TITLE:                    Synthesis and evaluation of novel aldose reductase
                          inhibitors: effects on lens protein kinase Cγ
AUTHOR(S):                Lewis, S.; Karrer, J.; Saleh, S.; Chen, Y.; Tan, Z.;
                          Hua, D.; McGill, J.; Pang, Y.-P.; Fenwick, B.;
                          Brightman, A.; Takemoto, D.
CORPORATE SOURCE:         Department of Biochemistry, Kansas State University,
                          Manhattan, KS, USA
SOURCE:                   Molecular Vision [online computer file] (2001), 7,
                          164-171
                          CODEN: MVEPFB; ISSN: 1090-0535
                          URL: http://www.molvis.org/molvis/v7/a23/lewis.pdf
PUBLISHER:                Molecular Vision
DOCUMENT TYPE:            Journal; (online computer file)
LANGUAGE:                 English
AB   The aim of the study was to synthesize novel aldose reductase inhibitors
```

(ARI) that will normalize losses in protein kinase Cγ (PKCγ) observed during diabetes and galactosemia. ARI were synthesized as tricyclic pyrones (HAR-1 through HAR-6) from 3-methyl-1H,7H-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran and (5aS,7S)-7-isopropenyl-3-methyl-1H,7H-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran and were tested by inhibition of aldose reductase enzyme activity in vitro and by inhibition of polyol formation in lens epithelial cells in culture. Identified compds. were further tested in galactosemic rat lens in vivo for (a) normalized PKCγ levels by Western blot, (b) reduction of phosphorylation of the gap junction protein Cx46 by analyses of co-immunopptd. proteins, and (c) by normalization of gap junction activity as measured by dye transfer. HAR-1 (1H,7H-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran-3-acetic acid) was identified as an ARI with IC50 for aldose reductase inhibition at 2 nM. Polyol accumulation in lens epithelial cells was reduced by 80% at 10 μM. Rats fed 40% galactose for 9 days had an 80% reduction in PKCγ levels which were normalized by HAR-1 at 100 mg/kg/day, fed orally. Phosphorylation of Cx46 was increased by 50% and this was normalized in HAR-1 treated rats (6 day treatment). Gap junction activity of galactosemic rats was reduced by 55% and this was normalized by HAR-1 in six day-treated rats. HAR-1 is a novel ARI which normalized losses of PKCγ, changes in Cx46 phosphorylation, and gap junction activity.

IT **434954-53-7P 434954-54-8P 434954-55-9P**
434954-56-0P 434954-57-1P 435269-05-9P
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and evaluation of novel aldose reductase inhibitors)

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> sel hit rn l9
E1 THROUGH E6 ASSIGNED

=> file reg
FILE 'REGISTRY' ENTERED AT 15:54:49 ON 02 FEB 2005

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 1 FEB 2005 HIGHEST RN 824390-04-7
DICTIONARY FILE UPDATES: 1 FEB 2005 HIGHEST RN 824390-04-7

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

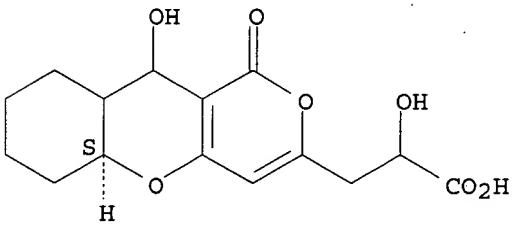
Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

```
=> s e1-e6
             1 434954-53-7/BI
               (434954-53-7/RN)
             1 434954-54-8/BI
               (434954-54-8/RN)
             1 434954-55-9/BI
               (434954-55-9/RN)
             1 434954-56-0/BI
               (434954-56-0/RN)
             1 434954-57-1/BI
               (434954-57-1/RN)
             1 435269-05-9/BI
               (435269-05-9/RN)
L12          6 (434954-53-7/BI OR 434954-54-8/BI OR 434954-55-9/BI OR 434954-56
               -0/BI OR 434954-57-1/BI OR 435269-05-9/BI)

=> d ide can l12 tot

L12  ANSWER 1 OF 6  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   435269-05-9  REGISTRY
CN   1H,7H-Pyrano[4,3-b][1]benzopyran-3-propanoic acid, 5a,6,8,9,9a,10-
     hexahydro-α,10-dihydroxy-1-oxo-, (5aS)- (9CI)  (CA INDEX NAME)
FS   STEREOSEARCH
MF   C15 H18 O7
SR   CA
LC   STN Files:   CA, CAPLUS, TOXCENTER
DT.CA  CAplus document type:  Journal
RL.NP  Roles from non-patents:  BIOL (Biological study); PREP (Preparation);
       USES (Uses)

Absolute stereochemistry.
```

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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

               1 REFERENCES IN FILE CA (1907 TO DATE)
               1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE   1:  137:15586

L12  ANSWER 2 OF 6  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   434954-57-1  REGISTRY
CN   1H,7H-Pyrano[4,3-b][1]benzopyran-3-acetic acid, 5a,6,8,9-tetrahydro-7-(2-
     hydroxy-1-methylethyl)-1-oxo-, (5aS,7S)- (9CI)  (CA INDEX NAME)
FS   STEREOSEARCH
MF   C17 H20 O6
SR   CA
LC   STN Files:   CA, CAPLUS, TOXCENTER
DT.CA  CAplus document type:  Journal
RL.NP  Roles from non-patents:  BIOL (Biological study); PREP (Preparation);
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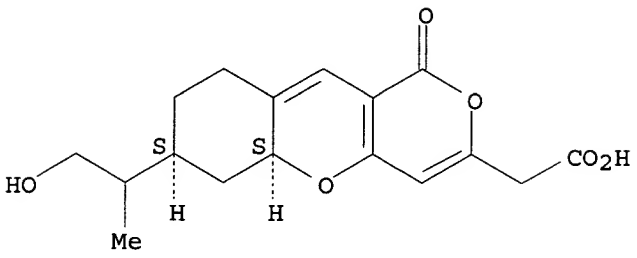
USES (Uses)

Absolute stereochemistry.



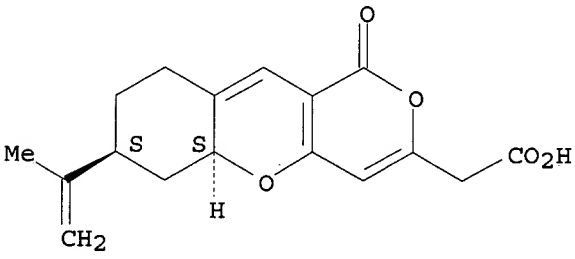
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:15586

L12 ANSWER 3 OF 6 REGISTRY COPYRIGHT 2005 ACS on STN
RN **434954-56-0** REGISTRY
CN 1H,7H-Pyrano[4,3-b][1]benzopyran-3-acetic acid, 5a,6,8,9-tetrahydro-7-(1-methylethenyl)-1-oxo-, (5aS,7S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C17 H18 O5
SR CA
LC STN Files: CA, CAPLUS, CASREACT, TOXCENTER
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

Absolute stereochemistry. Rotation (+).



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2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

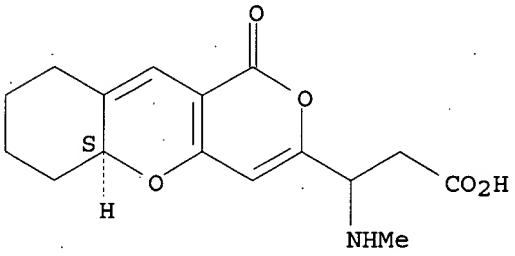
REFERENCE 1: 139:261078

REFERENCE 2: 137:15586

L12 ANSWER 4 OF 6 REGISTRY COPYRIGHT 2005 ACS on STN
RN **434954-55-9** REGISTRY

CN 1H,7H-Pyrano[4,3-b][1]benzopyran-3-propanoic acid, 5a,6,8,9-tetrahydro-β-(methylamino)-1-oxo-, (5aS)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C16 H19 N O5
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.



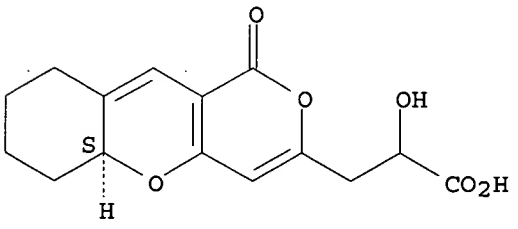
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:15586

L12 ANSWER 5 OF 6 REGISTRY COPYRIGHT 2005 ACS on STN
RN **434954-54-8** REGISTRY
CN 1H,7H-Pyrano[4,3-b][1]benzopyran-3-propanoic acid, 5a,6,8,9-tetrahydro-α-hydroxy-1-oxo-, (5aS)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C15 H16 O6
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.



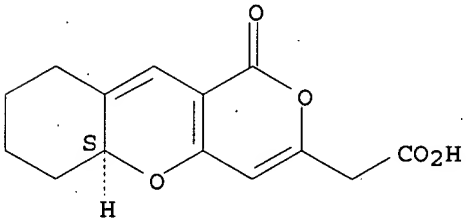
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:15586

L12 ANSWER 6 OF 6 REGISTRY COPYRIGHT 2005 ACS on STN
RN **434954-53-7** REGISTRY
CN 1H,7H-Pyrano[4,3-b][1]benzopyran-3-acetic acid, 5a,6,8,9-tetrahydro-1-oxo-, (5aS)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C14 H14 O5
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.



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REFERENCE 1: 141:388584

REFERENCE 2: 137:15586